

REMARKS

Claims 1, 2 and 4-41 are pending in the application. Claims 23-41 are withdrawn from consideration as being drawn to a non-elected invention. Claims 5-14 and 20 are withdrawn from consideration as being drawn to a non-elected species. Claim 4 has been amended to better clarify what Applicants believe to be the invention. Support for the amendment to claim 4 can be found throughout the specification, but particularly on page 45, lines 21-23, continuing on to page 46, lines 1-4. Accordingly, claims 1, 2, 4, 15-19, 21 and 22 remain under consideration.

***Claim Rejection under 35 U.S.C. §103(a)***A. Albert et al. in view of Kirberg et al. and Migita et al.

The rejection of claims 1, 2, 4, 15-17, 19, 21 and 22 under 35 U.S.C. §103(a), as being unpatentable over Albert et al (U.S. 2002/014396, priority to 09/251,896, filed February 19, 1999), in view of the abstract of Kirberg et al. (European Journal of Immunology, 1003, Vol. 23, pp. 1963-1967) and Migita et al. (J. Clin. Investigation, 1995, Vol. 96, pp. 727-732) is maintained for the reasons of record.

The Examiner fails to set forth a proper *prima facie* case of obviousness

Applicants remind the Examiner that a rejection under 35 U.S.C. §103 is proper only when a prior art reference alone or in combination with a second prior art reference renders the invention obvious. Applicants further remind the Examiner that a rejection based upon a combination of references is not proper unless the following three criteria are met: 1) the references in combination teach every single element of the invention as claimed; 2) there must be some suggestion or motivation in the prior art to combine the references to reach the invention as claimed; and 3) there must be a reasonable expectation of success in making the combination to reach the invention as claimed.

Any alleged combination of references in the present situation fails the most basic test for the appropriateness of a rejection. The Examiner admits that Albert et al. do not teach or suggest the induction of tolerance comprising the maturing of dendritic cells in the absence of CD+4 help. Furthermore, for the reasons outlined below, Applicants

assert that Albert et al. is not a proper reference under 35 U.S.C. §103(a), since both the Albert reference and the present application claim priority to the same applications. In addition, as shown below by Applicants' representatives, the remaining references simply cannot be combined in any way to result in the subject matter as claimed in the present application.

The present invention as claimed. The claims of the present application are drawn to methods for inducing tolerance in a mammal to an antigen comprising the steps of: isolating peripheral blood mononuclear cells (PBMC) from a whole blood sample from said mammal; isolating dendritic cells from said PBMC; **exposing said dendritic cells *ex vivo* to apoptotic cells expressing said antigen** in the presence of at least one dendritic cell maturation stimulatory molecule and in the absence of effective CD4+ T cell help, wherein said dendritic cells upon exposure to said dendritic cell maturation stimulatory molecule are characterized as having the phenotype CD14<sup>-</sup> and CD83<sup>+</sup>; and **introducing the dendritic cells into said mammal**; wherein said dendritic cells induce apoptosis of antigen-specific CD8+ T cells in said mammal resulting in tolerance to said antigen.

The dependent claims are drawn to particular dendritic cell maturation factors including PGE2, TNF-alpha, lipopolysaccharide, monocyte conditioned medium, CpG-DNA, or any combination thereof. Additional dependent claims are drawn to methods for exclusion of effective CD4+ T cell help by including at least one agent that inhibits or eliminates effective CD4+ T cell help. **The agent that inhibits or eliminates effective CD4+ T cell help is used to treat the dendritic cell and is washed out prior to exposure of the dendritic cell to the T cell.** Furthermore, the agent which inhibits or eliminates effective CD4 T cell help inhibits signaling consequent to dendritic cell-CD4 T cell engagement. Such an agent is selected from a FKBP antagonist and a TOR antagonist. The FKBP antagonist is tacrolimus. The TOR antagonist is rapamycin. The antigen is a tumor antigen, a viral antigen, a self-antigen or a transplant antigen. The dendritic cells are infused into the mammal after the dendritic cells mature and exhibit the phenotype CD14<sup>-</sup> and CD83<sup>+</sup> and the mammal is a human.

Albert et al. The Examiner alleges that Albert et al. teach a method for using apoptotic cells to deliver antigen to dendritic cells for tolerization of T cells and that dendritic cells are obtainable by culturing PBMCs with a combination of IL-4 and GM-CSF to promote differentiation into immature, antigen capturing dendritic cells. In addition, Albert et al. teach that the maturation of dendritic cells requires the presence of factors which include LPS, PGE2, TNF-alpha, IL-6, IL-1 beta, in addition to monocyte conditioned medium or necrotic cells. The Examiner further alleges that Albert et al. teach that the mature cells have the phenotype CD14-, CD83+ and HLA-Drhi. Furthermore, the Examiner alleges that Albert et al. teach that phagocytosis of apoptotic cells versus necrotic cells failed to mature the dendritic cells and that dendritic cells exposed to a mixture of apoptotic cells and necrotic cells induced similar increases in T cell stimulation as dendritic cells cultured with necrotic cells and that dendritic cells exposed in parallel to apoptotic cells and monocyte conditioned medium heightened T cell responses to the same extent as dendritic cells matured with monocyte conditioned medium, both experiments indicating that ingestion of apoptotic cells did not inhibit maturation or function of the dendritic cells. Furthermore, the Examiner alleges that phagocytosis of apoptotic cells may lead to T cell immunity if followed by a maturation signal and that signals provided by the necrotic cells such as TNF-alpha, IL-1 beta and IFN-gamma, inflammatory products such as LPS and CD+4 T cells would be required for the full activation of T cells. In addition, the Examiner alleges that Albert et al. cite publications which teach that model systems of cross-priming and cross-tolerance indicate that induction of CTL requires CD+4 help. As specifically noted by the Examiner, **Albert et al. do not teach the induction of tolerance comprising the maturing of dendritic cells in the absence of CD+4 help.**

Furthermore, Albert et al. **do not teach or suggest** the methods of the present invention for inducing tolerance. In particular, Albert et al. **do not teach that the absence of CD4+ T cell help, or the inhibition of CD4+ T cell help through the use of inhibitors of signaling consequent to dendritic cell-CD4+ T cell engagement is a requirement in conjunction with the generation of CD14- and CD83+ dendritic cells following addition of maturation factors** using the methods described in the present application for tolerance induction. In addition, Albert et al. do not teach the inhibition of signaling using agents such as those described herein, such as FK506 or rapamycin. More

particularly, Albert et al. **do not teach that the agents which inhibit signaling, such as those described in the present application, including FK506 or rapamycin, may be used to treat the dendritic cell, and is washed out prior to exposure of the dendritic cell to the T cell.**

Albert et al. is not a prior art reference under 35 U.S.C. §102

More importantly, Applicants' representatives assert that the Albert reference (U.S. 2002/0146396, priority to 09/251,896, filed February 19, 1999) is an improper reference under 35 U.S.C. §102, and thus cannot serve as the basis for a rejection under 35 U.S.C. §103(a), since the publication is based on a continuation application having U.S. serial number 09/251,896, filed on February 19, 1999, which is the same application to which the present application claims priority. Proof of this can be found in the enclosed copies of the Filing Receipts, one from the present application, serial number 09/804,584, and one from the continuation application, serial number 10/014,877 (U.S. publication number 2002/0146396), both attached herewith for the convenience of the Examiner. In light of the foregoing, Applicants' representatives assert that the Albert et al. publication is an improper reference under 35 U.S.C. 103(a) and on this basis respectfully request withdrawal of this rejection.

The Examiner has objected to the amendment filed May 27, 2003 under 35 U.S.C. 132 because it allegedly introduces new matter into the disclosure. Applicants' representatives respectfully point out to the Examiner that the priority data, included in the amendment and response to the Office Action dated February 27, 2003, for which a response was filed on May 27, 2003, is not new matter. The present application clearly claims the right to priority as shown in the attached Filing Receipts. Furthermore, the text of the present application as filed incorporates both U.S. serial numbers 09/565,958, filed May 5, 2000 and 09/251,896, filed Feb. 19, 1999 by reference in their entireties. In addition, U.S. serial number 09/251,896, for which the Filing Receipt is also attached herewith, clearly claims priority to and incorporates by reference in their entireties all three provisional patent applications, Serial No. 60/075,356, filed February 20, 1998; Serial No. 60/077,095, filed March 6, 1998 and Serial No. 60/101,749, filed September

24, 1998. Applicants respectfully request that the new matter objection be withdrawn in light of the support for the priority claims provided herewith.

Kirberg et al. The Kirberg et al. reference teaches that CD4+ T cell help in the form of interleukin-2 delays the deletion of CD8+ T cells after transient response to antigen.

Kirberg et al. **do not teach or suggest** the methods of the present invention. In particular, Kirberg et al. **do not teach that the presentation of antigen by apoptotic cells to the dendritic cell *ex vivo* with a dendritic cell maturation factor in the absence of CD4+ T cell help results in induction of tolerance**. In particular, Kirberg et al. **do not teach** that following exposure of the dendritic cells to a maturation stimulus in the absence of CD4+ T cell help results in **generation of a population of dendritic cells expressing high levels of surface expression of CD83<sup>+</sup>, but which are CD14<sup>-</sup>**. Kirberg et al. also do not teach that introducing the dendritic cells having these markers into a mammal results in induction of apoptosis of antigen-specific CD8+ T cells in the mammal resulting in tolerance to the antigen. In addition, Kirberg et al. **do not contemplate treating dendritic cells with agents that inhibit or eliminate effective CD4+ T cell help, such as FK506 or rapamycin**, then washing the dendritic cells to remove these agents, which inhibit or eliminate effective CD4+ T cell help by inhibiting signaling consequent to dendritic cell-CD4+ T cell engagement.

Migita et al. Migita et al. teach that FK506 enhances the apoptotic effect of anti-CD3 antibody.

Migita et al. **do not teach or suggest** the methods of the present invention. In particular, Migita et al. **do not teach that the presentation of antigen by apoptotic cells to the dendritic cell with a dendritic cell maturation factor in the absence of CD4+ T cell help results in induction of tolerance**. In particular, Migita et al. **do not teach** that following exposure of dendritic cells *ex vivo* to a maturation stimulus in the absence of CD4+ T cell help results in **generation of a population of dendritic cells expressing high levels of surface expression of CD83<sup>+</sup> but which are CD14<sup>-</sup>**. Furthermore, Migita et al. **do not teach** that the agents of the present invention, eg. tacrolimus or rapamycin, which inhibits or eliminates effective CD4+ T cell help, does so by inhibiting signaling

**consequent to dendritic cell-CD4+ T cell engagement.** More specifically, **Migita et al. do not teach that the dendritic cells are treated with the agents such as FK506 or rapamycin *ex vivo*, followed by a washing step to remove the agent before the dendritic cell is exposed to the T cell.**

The Argument for Non-obviousness based on the combined teachings of Albert et al. in view of Kirberg et al. and Migita et al.

As noted above, Applicants' representatives assert that Albert et al. is an improper reference under 35 U.S.C. §103(a) in light of the proper and **common** claim to priority, as demonstrated by the enclosed Filing Receipts. Accordingly, Applicants further assert that on this basis, the references of Kirberg et al. and Migita et al., when considered alone, do not teach or suggest the subject matter as claimed in the present application for inducing tolerance by exposing dendritic cells to antigen in the context of an apoptotic cell *ex vivo*, in the presence of at least one dendritic cell maturation stimulatory molecule and in the absence of effective CD4+ T cell help. While Applicants believe that the teachings of Albert et al. do not extend to the methods of inducing tolerance, as shown by the present application, Applicants further assert that even if Albert et al. were a proper reference under 35 U.S.C. §103(a), there would still be no reasonable expectation of success, when combined with Kirberg et al. and Migita et al.. More particularly, Applicants assert that neither the Albert et al. reference nor the Kirberg et al. reference nor the Migita et al. reference teach or suggest that dendritic cells, when exposed *ex vivo* to antigen presented in the context of an apoptotic cell, and in the presence of agents that induce maturation of the dendritic cell but in the absence of T cell help, followed by reintroduction of these dendritic cells to a mammal, results in apoptosis of antigen specific T cells.

Moreover, it is Applicants' belief that the Examiner is misunderstanding the basic concept of the invention in that one of the mechanisms used to block T cell help is through **use of an agent such as FK506 or rapamycin for treating the dendritic cell with such agent, not the T cell.** Applicants are not inducing apoptosis of the antigen specific T cell by treating the T cell with FK506 or rapamycin. Applicants are treating the dendritic cell with FK506 or rapamycin, followed by a wash-out of the

drug prior to reintroducing the cells to the mammal. Support for this can be found in the instant application on page 45, lines 21-23, continuing on to page 46, lines 1-4.

B. Albert et al., Kirberg et al., Migita et al. and Matzinger et al. further in view of Li et al. and Sehgal et al.

The rejection of claims 1, 2, 4, 15-19, 21 and 22 under 35 U.S.C. 103(a) as being unpatentable over Albert et al (U.S. 2002/014396, priority to 09/251,896, filed February 19, 1999), in view of the abstract of Kirberg et al. (European Journal of Immunology, 1003, Vol. 23, pp. 1963-1967) and Matzinger (Annual review of Immunology, 1994, Vol. 12, pp. 991-1045) and Migita et al. (J. Clin. Investigation, 1995, Vol. 96, pp. 727-732) as applied to claims 1, 2, 4, 15-17, 19, 21 and 22 above and further in view of Li et al. (Transplantation 1998, Vol. 66, pp. 1387-1388) and Sehgal et al. (Clin. Biochemistry, 1998, Vol. 31, pp. 335-340) is maintained.

The teachings of Albert et al, Kirberg et al. and Migita et al are summarized above. Furthermore, the reasons submitted by Applicants for the improper use of Albert et al. as a reference under 35 U.S.C. 103(a) are also noted above.

Matzinger et al. Matzinger et al. teach that cytotoxic T lymphocytes become unresponsive to antigen if the cytotoxic T lymphocyte encounters antigen first in the absence of CD+4 T cell help.

Matzinger et al. **do not teach or suggest** the methods of the present invention. More particularly, Matzinger et al. **do not teach** that presentation of antigen for which tolerance is desired to dendritic cells via apoptotic cells, in the presence of a dendritic cell maturation factor, but in the absence of T cell help using agents such as tacrolimus or rapamycin, results in **generation of dendritic cells having a phenotype of CD14<sup>+</sup> and CD83<sup>+</sup>, which when administered to a subject results in apoptosis of antigen specific T cells.** Matzinger et al. **do not teach** that the agents of the present invention, *eg.* tacrolimus or rapamycin, which inhibits or eliminates effective CD4<sup>+</sup> T cell help, does so by inhibiting signaling **consequent to dendritic cell-CD4<sup>+</sup> T cell engagement.** Furthermore, more importantly, Matzinger et al. **do not teach that the dendritic cell is**

**exposed to the agents such as FK506 or rapamycin, and that these agents are washed out prior to exposure to T cells.** Thus, the effect of these agents is on the dendritic cell, not the T cell.

**Li et al.** Li et al. teach that tolerance to an allograft may be induced using **rapamycin as adjunct therapy with a co-stimulation blockade** (anti-CD40 ligand plus CTLA-4Ig). Furthermore, **Li et al. teach that rapamycin blocks IL-2 induced proliferation, but not apoptotic signals to achieve tolerance to an antigen.**

**Li et al. do not teach or suggest** the methods of the present invention. In particular, Li et al. do not teach the presentation of antigen for which tolerance is desired via apoptotic cells to dendritic cells in the presence of a dendritic cell maturation factor, but in the absence of CD4+ T cell help. More particularly, Li et al. do not teach the methods of the present invention which result in the generation of a population of CD14<sup>+</sup>, CD83<sup>+</sup> dendritic cells, which when administered to a human subject result in apoptosis of antigen specific T cells. Furthermore, Li et al. do not teach that the agents of the present invention, eg. FK506 or rapamycin, which inhibit or eliminate effective CD4+ T cell help, do so by **inhibiting signaling consequent to dendritic cell-CD4+ T cell engagement**. Thus, **Li et al. do not teach that the dendritic cell is exposed to the agents such as FK506 or rapamycin, and that these agents are washed out prior to exposure to T cells.** Thus, the effect of these agents is on the dendritic cell, not the T cell.

**Sehgal** Sehgal teaches that rapamycin complexes with the immunophilin FKBP to produce the mammalian inhibitor of rapamycin complex which blocks the IL-2 mediated signal transduction pathway that prevents cell cycle progression from G1 to S phase **in T cells.**

**Sehgal does not teach or suggest** the methods of the present invention. In particular, Sehgal does not teach the presentation of antigen for which tolerance is desired via apoptotic cells to dendritic cells in the presence of a dendritic cell maturation factor, but in the absence of CD4+ T cell help. More particularly, Sehgal does not teach the methods of the present invention which result in the generation of a population of CD14<sup>+</sup>,

CD83<sup>+</sup> dendritic cells, which when administered to a human subject result in apoptosis of antigen specific T cells. Furthermore, **Sehgal does not teach or suggest that treating the dendritic cells with FK506 or rapamycin *ex vivo*, followed by washing out these drugs before reintroducing the dendritic cells into a mammal results in apoptosis of antigen specific T cells.** In addition, **the target of RAPA:FKBP is distinct from calcineurin**, unlike FK506, which when complexed with its respective immunophilin inhibits calcineurin, which is required for early T cell activation. Sehgal **does not teach or suggest that the effect of FK506 or rapamycin is on the dendritic cell, not the T cell.**

The Argument for Non-obviousness based on the combined teachings of Albert et al. in view of Li et al. and Sehgal

As noted above, Applicants assert that the Albert et al. reference cannot serve as a proper reference for a rejection under 35 U.S.C. 103(a) since the present application and the Albert et al. reference both claim priority to the same parent application, proof of which has been provided to the Examiner by way of the enclosed Filing Receipts.

Furthermore, any rejection based on Li *et al.* alone or in combination with Sehgal fails for the following reasons:

1. There simply is no teaching or suggestion of tolerance induction by presenting antigen to dendritic cells via apoptotic cells in the presence of dendritic cell maturation factors, but in the absence of CD4+ T cell help, which results in the generation of dendritic cells bearing the phenotype CD14<sup>-</sup> and CD83<sup>+</sup>, which upon transfer to a subject results in apoptosis of antigen specific CD8+ T cells.
2. Furthermore, there is no teaching or suggestion that the absence of CD4+ T cell help could be substituted by **treating the dendritic cells with FK506 or rapamycin, and washing out the drug prior to reintroduction of the dendritic cells to a mammal.**
3. Furthermore, there is no teaching or suggestion that a specific action of such inhibitors of signaling on a reconstituted system consisting of dendritic cells and apoptotic cells, provides a long-lasting effect on those dendritic cells

such that they are now "inhibitory/tolerizing" even with subsequent encounter to CD4.

4. Furthermore, there is no teaching or suggestion that the dendritic cells could be treated with an agent such as FK506 or rapamycin *ex vivo* followed by washing out the drug prior to readministration to a mammal, which results in tolerance induction.

The Argument for Non-obviousness based on the combined teachings of Kirberg et al. in view of Li et al. and Sehgal

As noted previously, Kirberg et al. teach that CD+4 T cell help in the form of interleukin-2 delays the deletion of CD+8 T cells after transient response to antigen. Li et al. teach that tolerance to an allograft may be induced using **rapamycin as adjunct therapy with a co-stimulation blockade** (anti-CD40 ligand plus CTLA-4Ig).

Furthermore, **Li et al. teach that rapamycin blocks IL-2 induced proliferation, but not apoptotic signals to achieve tolerance to an antigen.** Sehgal teaches that rapamycin complexes with the immunophilin FKBP to produce the mammalian inhibitor of rapamycin complex which blocks the IL-2 mediated signal transduction pathway that prevents cell cycle progression from G1 to S phase **in T cells.**

Furthermore, any rejection based on Kirberg et al alone or in combination with Li *et al.* or in combination with Sehgal fails for the following reasons:

1. There simply is no teaching or suggestion of tolerance induction by presenting antigen to dendritic cells via apoptotic cells in the presence of dendritic cell maturation factors, but in the absence of CD4+ T cell help, which results in the generation of dendritic cells bearing the phenotype CD14<sup>-</sup> and CD83<sup>+</sup>, which upon transfer to a subject results in apoptosis of antigen specific CD8+ T cells.
2. Furthermore, there is no teaching or suggestion that the absence of CD4+ T cell help could be substituted **by treating the dendritic cells with FK506 or rapamycin, and washing out the drug prior to reintroduction of the dendritic cells to a mammal.**

3. Furthermore, there is no teaching or suggestion that a specific action of such inhibitors of signaling on a reconstituted system consisting of dendritic cells and apoptotic cells, provides a long-lasting effect on those dendritic cells such that they are now "inhibitory/tolerizing" even with subsequent encounter to CD4.
4. Furthermore, there is no teaching or suggestion that the dendritic cells could be treated with an agent such as FK506 or rapamycin *ex vivo* followed by washing out the drug prior to readministration to a mammal, which results in tolerance induction.

The Argument for Non-obviousness based on the combined teachings of Matzinger et al. in view of Li et al. and Sehgal

As noted above, Matzinger et al. teach that cytotoxic T lymphocytes become unresponsive to antigen if the cytotoxic T lymphocyte encounters antigen first in the absence of CD+4 T cell help. Li et al. teach that tolerance to an allograft may be induced using **rapamycin as adjunct therapy with a co-stimulation blockade** (anti-CD40 ligand plus CTLA-4Ig). Furthermore, **Li et al. teach that rapamycin blocks IL-2 induced proliferation, but not apoptotic signals to achieve tolerance to an antigen.** Sehgal teaches that rapamycin complexes with the immunophilin FKBP to produce the mammalian inhibitor of rapamycin complex which blocks the IL-2 mediated signal transduction pathway that prevents cell cycle progression from G1 to S phase in **T cells.**

Furthermore, any rejection based on Matzinger et al alone or in combination with Li *et al.* or in combination with Sehgal fails for the following reasons:

1. There simply is no teaching or suggestion of tolerance induction by presenting antigen to dendritic cells via apoptotic cells in the presence of dendritic cell maturation factors, but in the absence of CD4+ T cell help, which results in the generation of dendritic cells bearing the phenotype CD14<sup>-</sup> and CD83<sup>+</sup>, which upon transfer to a subject results in apoptosis of antigen specific CD8+ T cells.
2. Furthermore, there is no teaching or suggestion that the absence of CD4+ T cell help could be substituted by treating the dendritic cells with FK506 or

**rapamycin, and washing out the drug prior to reintroduction of the dendritic cells to a mammal.**

3. Furthermore, there is no teaching or suggestion that a specific action of such inhibitors of signaling on a reconstituted system consisting of dendritic cells and apoptotic cells, provides a long-lasting effect on those dendritic cells such that they are now "inhibitory/tolerizing" even with subsequent encounter to CD4.
4. Furthermore, there is no teaching or suggestion that the dendritic cells could be treated with an agent such as FK506 or rapamycin *ex vivo* followed by washing out the drug prior to readministration to a mammal, which results in tolerance induction.

The Argument for Non-obviousness based on the combined teachings of Migita et al. in view of Li et al. and Sehgal

As noted previously, Migita et al. teach that FK506 enhances the apoptotic effect of anti-CD3 antibody. Li et al. teach that tolerance to an allograft may be induced using **rapamycin as adjunct therapy with a co-stimulation blockade** (anti-CD40 ligand plus CTLA-4Ig). Furthermore, **Li et al. teach that rapamycin blocks IL-2 induced proliferation, but not apoptotic signals to achieve tolerance to an antigen.** Sehgal teaches that rapamycin complexes with the immunophilin FKBP to produce the mammalian inhibitor of rapamycin complex which blocks the IL-2 mediated signal transduction pathway that prevents cell cycle progression from G1 to S phase in T cells.

Furthermore, any rejection based on Matzinger et al alone or in combination with Li *et al.* or in combination with Sehgal fails for the following reasons:

1. There simply is no teaching or suggestion of tolerance induction by presenting antigen to dendritic cells via apoptotic cells in the presence of dendritic cell maturation factors, but in the absence of CD4+ T cell help, which results in the generation of dendritic cells bearing the phenotype CD14<sup>-</sup> and CD83<sup>+</sup>, which upon transfer to a subject results in apoptosis of antigen specific CD8+ T cells.

2. Furthermore, there is no teaching or suggestion that the absence of CD4+ T cell help could be substituted by treating the dendritic cells with FK506 or rapamycin, and washing out the drug prior to reintroduction of the dendritic cells to a mammal.
3. Furthermore, there is no teaching or suggestion that a specific action of such inhibitors of signaling on a reconstituted system consisting of dendritic cells and apoptotic cells, provides a long-lasting effect on those dendritic cells such that they are now "inhibitory/tolerizing" even with subsequent encounter to CD4.
4. Furthermore, there is no teaching or suggestion that the dendritic cells could be treated with an agent such as FK506 or rapamycin *ex vivo* followed by washing out the drug prior to readministration to a mammal, which results in tolerance induction.

The analysis under § 103(a). As noted above, Applicants assert that Albert et al. is not a proper reference under 35 U.S.C. §102 or §103(a), due to the fact that the present application and the Albert et al. patent publication claim priority to a common application. Thus, Applicants further assert that the remaining references alone or in combination with each other do not teach or suggest the methods disclosed in the present application for tolerance induction. Moreover, since the methods described in the present application for tolerance induction were unknown at the time of the references cited, it was not possible to predict the steps and conditions necessary to optimize induction of antigen specific tolerance. Moreover, it was not until Applicants' present invention that the precise steps involved in tolerance induction by presenting antigen to dendritic cells via apoptotic cells *ex vivo* in the presence of dendritic cell maturation factors, but in the absence of CD4+ T cell help, which then resulted in the generation of dendritic cells bearing the phenotype CD14<sup>-</sup> and CD83<sup>+</sup>, which upon transfer to a mammal resulted in apoptosis of antigen specific CD8+ T cells, were identified. Furthermore, it was not until the time of Applicants' own research that it was realized that the absence of CD4+ T cell help could be substituted by first treating the dendritic cell with an inhibitor of signaling, such as with FK506 or rapamycin, then washing out the inhibitor prior to exposure to the T cell. In addition, the present invention teaches, and no prior art

suggests, that a specific action of such inhibitors of signaling on a reconstituted system consisting of dendritic cells and apoptotic cells, **provides a long-lasting effect on those dendritic cells such that they are now "inhibitory/tolerizing" even with subsequent encounter to CD4.**

In light of the foregoing claim amendments and arguments, Applicants respectfully request withdrawal of the rejection.

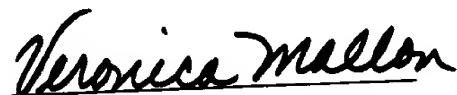
*Fees*

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

*Conclusion*

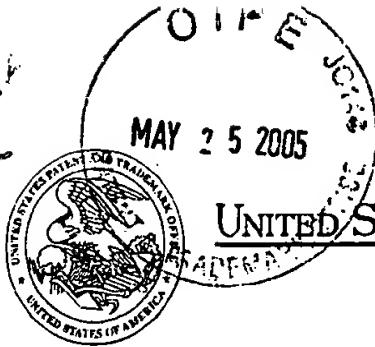
Applicants believe that in view of the foregoing, the claims are in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

  
Veronica Mallon, Ph.D.  
Agent for Applicants  
Registration No. 52,491

KLAUBER & JACKSON  
411 Hackensack Avenue  
Hackensack, NJ 07601  
(201) 487-5800

Attachments: 4 Filing Receipts for :  
USSN 09/804,584  
USSN 09/565,958  
USSN 10/014,877  
USSN 09/251,896



**UNITED STATES PATENT AND TRADEMARK OFFICE**

COMMISSIONER FOR PATENTS  
UNITED STATES PATENT AND TRADEMARK OFFICE  
WASHINGTON, D.C. 20231  
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/804,584	03/12/2001	1633	609	600-1-276 CIP	19	41	2

**CONFIRMATION NO. 5033**

23565  
KLAUBER & JACKSON  
411 HACKENSACK AVENUE  
HACKENSACK, NJ 07601

**CORRECTED FILING RECEIPT**



\*OC000000007307258\*

Date Mailed: 01/14/2002

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

**Applicant(s)**

Matthew L. Albert, New York, NY;  
Mithila Jegathesan, New York, NY;  
Robert B. Darnell, Pelham, NY;

**RECEIVED**

JAN 10 2002

**Domestic Priority data as claimed by applicant**

THIS APPLICATION IS A CIP OF 09/565,958 05/05/2000  
AND A CIP OF 09/251,896 02/19/1999

KLAUBER & JACKSON

**Foreign Applications**

**If Required, Foreign Filing License Granted 05/23/2001**

**Projected Publication Date:** Not Applicable

**Non-Publication Request:** No

**Early Publication Request:** No

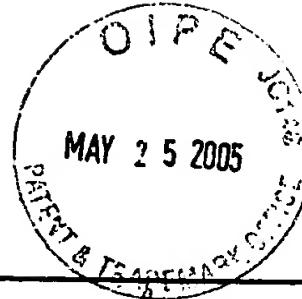
**Title**

Methods for abrogating a cellular immune response

**Preliminary Class**



UNITED STATES PATENT AND TRADEMARK OFFICE



COMMISSIONER FOR PATENTS  
UNITED STATES PATENT AND TRADEMARK OFFICE  
WASHINGTON, D.C. 20231  
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/565,958	05/05/2000	1614	1946	600-1-276	12	143	14

23565  
KLAUBER & JACKSON  
411 HACKENSACK AVENUE  
HACKENSACK, NJ 07601

**FILING RECEIPT**



\*OC00000005499371\*

Date Mailed: 10/24/2000

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

**Applicant(s)**

RECEIVED

Matthew Albert, New York, NY ;  
Raymond Birge, New York, NY ; OCT 27 2000

**Continuing Data as Claimed by Applicant** KLAUBER & JACKSON  
THIS APPLICATION IS A CIP OF 09/251,896 02/19/1999

**Foreign Applications**

**If Required, Foreign Filing License Granted 07/10/2000**

**\*\* SMALL ENTITY \*\***

**Title**

Genetic manipulation of phagocytes for modulation of antigen processing and the immune response therefrom

**Preliminary Class**

514

**Data entry by : HALL, ELMIRA**

**Team : OIPE**

**Date: 10/24/2000**





UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS  
UNITED STATES PATENT AND TRADEMARK OFFICE  
WASHINGTON, D.C. 20231  
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/014,877	12/11/2001	1642	1106	600-1-291 CON	41	48	9

23565  
KLAUBER & JACKSON  
411 HACKENSACK AVENUE  
HACKENSACK, NJ 07601

RECEIPT  
MAY 25 2005  
TRADEMARKS  
Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

**CONFIRMATION NO. 4555**

**UPDATED FILING RECEIPT**



\*OC000000007678644\*

Date Mailed: 03/20/2002

**Applicant(s)**

Matthew L. Albert, New York, NY;  
Nina Bhardwaj, West Orange, NJ;  
Ralph M. Steinman, Westport, CT;  
Kayo Inaba, Kyoto, JAPAN;

**Domestic Priority data as claimed by applicant**

THIS APPLICATION IS A CON OF 09/251,896 02/19/1999  
WHICH CLAIMS BENEFIT OF 60/075,356 02/20/1998  
AND CLAIMS BENEFIT OF 60/077,095 03/06/1998  
AND CLAIMS BENEFIT OF 60/101,749 09/24/1998

**Foreign Applications**

If Required, Foreign Filing License Granted 01/31/2002

Projected Publication Date: 06/27/2002

Non-Publication Request: No

Early Publication Request: No

\*\* SMALL ENTITY \*\*

Title

100-1-291  
MAY 25 2005  
RECEIVED & INDEXED

FILING RECEIPT  
CORRECTED



UNITED STATES DEPARTM. OF COMMERCE  
Patent and Trademark Office  
ASSISTANT SECRETARY AND COMMISSIONER  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
09/251,896	02/19/99	1642	\$1,127.00	2016-4014US3	R36	48	10

MORGAN & FINNEGAN LLP  
345 PARK AVENUE  
NEW YORK NY 10154

RECEIVED  
NOV - 8 A 10:26  
MORAN & FINNEGAN LLP  
BUCKET DEPT.

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts of Application" ("Missing Parts Notice") in this application, please submit any corrections to this Filing Receipt with your reply to the "Missing Parts Notice." When the PTO processes the reply to the "Missing Parts Notice," the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s) MATTHEW L. ALBERT, NEW YORK, NY; NINA BHARDWAJ, WEST ORANGE, NJ; RALPH M. STEINMAN, WESTPORT, CT; KAYO INABA, KYOTO, JAPAN.

CONTINUING DATA AS CLAIMED BY APPLICANT-

PROVISIONAL APPLICATION NO. 60/075,356 02/20/98  
PROVISIONAL APPLICATION NO. 60/077,095 03/06/98  
PROVISIONAL APPLICATION NO. 60/101,749 09/24/98

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 03/12/99 \*\* SMALL ENTITY \*\*  
TITLE

METHODS FOR USE OF APOPTOTIC CELLS TO DELIVER ANTIGEN TO DENDRITIC CELLS FOR INDUCTION OR TOLERIZATION OF T CELLS

PRELIMINARY CLASS: 424

CASE 2016-4014US3 ATTY SAL  
INFORMATION DISCLOSURE STATEMENT \_\_\_\_\_  
FOREIGN FILING \_\_\_\_\_  
CONVENTION DATE EXPIRES \_\_\_\_\_

DATA ENTRY BY: WILSON, PAMELLA

TEAM: 12 DATE: 11/02/99



(See reverse for new important information)